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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D C 20460

MAY 7 1990

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Subject: EPA ID # 7969-53. DER for The Full Report of Four Developmental Toxicity Studies of Vinclozolin in the rat/BASF # 89-0130, Report Project # 89-0090, 89-0091, 89-0092, and 89-0093; Project #: 34R0165/84084, 34R0165/84085, 34R0165/84086, and 92R0165/84088, respectively. (MRID No. 411322-01).

Tox. Chem. No.: 323C.
Project No.: 9-1640.
Record No.: 246906.

To: S Lewis/J Stone, PM 21
Registration Division (H7505C)

From: David G Anderson, PhD. David G Anderson 4/25/90
Section 2, Toxicology Branch I (IRS)
Health Effects Division (H7509C)

Thru: Marion Copley, DVM Marion Copley 4/30/90
Section Head, Section 2
Toxicology Branch I (IRS)
Health Effects Division (H7509C).

CONCLUSIONS:

This is a final report on four developmental toxicity studies and confirms the results from a previously reported preliminary studies of these effects (MRID # 409505-01, HED Document 007228).

Gavage administration of Vinclozolin to pregnant rats results in decreased anal-genital distance in males at 50 mg/kg/day with a NOEL of 15 mg/kg/day.

CONCLUSIONS: This DER contains 4 studies reviewed together. The 4 studies or projects are referred to by the last number in the project number (See Tables A, B, C, and D below).

Doses Administered: In study 4 - 0, 15, 50, and 150 mg/kg/day, in study 5 - 0, 50, 100, and 200 mg/kg/day, in study 6 - 0, 200, and 400 mg/kg/day, and in study 8 - 0, 600, and 1000 mg/kg/day.

4/25

Developmental Toxicity:
NOEL: 15 mg/kg/day.
LEL: 50 mg/kg/day for decreased anal-genital distance and anal-genital index in males (pseudohermaphroditism). Increased incidence of dilated renal pelvis, hydroureter, and accessory 14th rib may have occurred at 400 mg/kg/day and higher.

Maternal Toxicity:
NOEL: < 600 mg/kg/day.
LEL: < 600 mg/kg/day for increases in absolute and relative adrenal and liver weight. Organ weights were not determined at lower dose levels.

Core classification: Supplementary until a satisfactory data is submitted on the stability of the test material in 0.5% CMC.

Requested Action:

The Registration Division requested that the Toxicology Branch I (IRS) review data on four developmental toxicity studies with Vinclozolin.

Additional Needed Information:

The stability of Vinclozolin in 0.5% CMC was reported to be 80% in 24 hours at room temperature with only a summary statement about a metabolite being increased in proportion. Submission of stability data is required. However, data on the stability of Vinclozolin in 0.5% CMC has been requested for the dermal developmental toxicity study. If this information about the dermal developmental toxicity study is acceptable, it also would be acceptable and sufficient for this current gavage developmental study.

Cover memo on the full report of four developmental toxicity studies/Rat/B:\VINCL723.23C\ MDEV4CO.FUL/D Anderson/4/23/90.

Primary reviewer: David G Anderson, PhD. David G Anderson 4/30/90
Section 2, Tox. Branch 1 (H7509C).
Secondary reviewer: Marion Copley, DVM. Marion Copley 4/30/90
Section 2, Tox. Branch 1 (H7509C).

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DATA EVALUATION REPORT

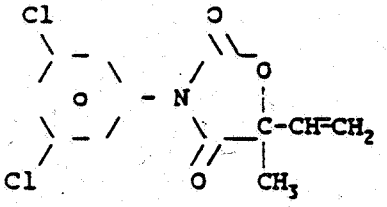
STUDY TYPE: Developmental Toxicity/83-3/Rat/BASF Proj. # 89-0190, Report Proj. # 89-0090, 89-0091, 89-0092, and 89-0093; Project Nos: 34R0165/84084, 34R0165/84085, 34R0165/84086, and 92R0165/84088, respectively.

TOX. CHEM. No.: 323C

MRID No.: 411322-01

TEST MATERIAL: Vinclozolin, technical; A.I. is [3-(3,5-dichlorophenyl)-5-ethenyl-5-methyl-2,4-oxazolidinedi-2,4-one].

STRUCTURE:



SYNONYMS: Ronilan.

SPONSOR: BASF Corp. Chemicals Div., Ag. Chem., 100 Cherry Hill Road, Parsippany, NJ 07054.

TESTING FACILITY: BASF Aktiengesellshaft, Dept. Toxicology, 6700 Ludwigshafen, Federal Republic of Germany.

STUDY NO.: BASF No. 89-0190, Report Projects Nos.: 89-0090, 89-0091, 89-0092, and 89-0093. 89-0090 was project #: 34R0165/84084, 89-0091 was project #: 34R0165/84085, 89-0092 was project #: 34R0165/84086, and 89-0093 was project #: 92R0165/84088. Project # 89-0493; The First Preliminary Results of Several....., which was presented in Doc. No. 7228, consisting of Study #: 88/0493, Project #: 34R0165/84084, 34R0165/84085, 34R0165/84086, 92R0165/84088.

REPORT TITLE: Report on the Prenatal Toxicity Studies with Reg. No. 83 258 (Vinclozolin) in Rats After Oral Administration (Gavage) - Consisting of Report Nos. 89/0090, 89/0091, (89/0092) (This latter number was omitted from title), 89/0093.

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Developmental Toxicity/83-3/Rat/BASF # 89-0190.

AUTHOR(S): J Hellwing (Sic), PhD. (Author in preliminary studies and on page 17 of 411322-01 was listed as J Hellwig, PhD).

REPORT ISSUED: March, 1989.

CONCLUSIONS: This DER contains 4 studies reviewed together. The four studies or projects are referred to by the last number of the project (See Tables A, B, C, and D below).

Doses Administered: In study 4 - 0, 15, 50, and 150 mg/kg/day, in study 5 - 0, 50, 100, and 200 mg/kg/day, in study 6 - 0, 200, and 400 mg/kg/day, and in study 8 - 0, 600, and 1000 mg/kg/day.

Developmental Toxicity:
NOEL: 15 mg/kg/day.
LEL: 50 mg/kg/day for decreased anal-genital distance in males (pseudohermaphroditism). Increased incidence of dilated renal pelvis, hydroureter, and accessory 14th rib may have occurred at 400 mg/kg/day and higher.

Maternal Toxicity:
NOEL: < 600 mg/kg/day.
LEL: < 600 mg/kg/day for increases in absolute and relative adrenal and liver weight. Organ weights were not determined at lower dose levels.

Core classification: Supplementary until a satisfactory data is submitted on the stability of the test material in 0.5% CMC.

A. MATERIALS:

1. Test compound:Vinclozolin, Description: Solid white powder, Test Substance # 34/165, Batch # N173, Purity 99.6%.

2. Test animals: Species:Rats, Strain: Chbb:THOM-SPF Wistar, Age: 9-10 weeks, Weight: mean = 221 g at mating, Source: Karl Thomae, Biberach an der Riss. FRG. Acclimatization: > 5 days.

3. Environmental: Housing: single caging, stainless steel wire mesh. Temperature: 20 - 24 degrees C. Humidity: 30 - 70%. Light:dark = 12:12.

B. STUDY DESIGN: The 4 studies under study report numbers 89-0090, 89-0091, 89-0092, and 89-0093 were conducted from September 21 to October 19, 1987; January 11 to February 11, 1988; March 30 to April 27, 1988; and May 26 to June 15, 1988, respectively. These studies will be referred to in the subsequent report by the last number of each corresponding project #.

89-0090 is project #: 34R0165/940841,

Developmental Toxicity/83-3/Rat/BASF # 89-0190.

89-0091 is project #: 34R0165/84085,
89-0092 is project #: 34R0165/84086, and
89-0093 is project #: 92RC165/84088.

1. Animal Assignment - The animals were randomly assigned and animals ear tagged. Females were co-housed with males, 2-4:1. There was no indication that males were assigned to an equal number of females/group.

2. Test Substance Administration: Test substance was administered by gavage in 5 ml of 0.5% carboxylmethylcellulose in distilled water/kg body weight and extended from gestational day (gd) 6 to gd 19 because of nature of the effects produced. The Guidelines 83-3 require administration of the doses from gestational day (gd) 6 to 15. The dose levels and the number of animals used per group in the four studies are given in Tables A, B, C, and D.

Table A.

Groups used for Project Number 34R0165/84084. Hereafter designated Study 4.

Test group	Dose mg/kg/day	Volume of Doses ml/kg/day	Conc. in mg/100 ml	Number of Females
1. Cont.	0.5% CMC in water vehicle	5	0	25
2. Low (LDT)	15	5	300	25
3. Mid (MDT)	50	5	1000	25
4. High(HDT)	150	5	3000	25

Table B.

Groups used for Project Number 34R0165/84085. Hereafter designated Study 5.

Test group	Dose mg/kg/day	Volume of Doses ml/kg/day	Conc. in mg/100 ml	Number of Females
1. Cont.	0.5% CMC in water vehicle	5	0	25
2. Low (LDT)	50	5	1000	25
3. Mid (MDT)	100	5	2000	25
4. High(HDT)	200	5	4000	25

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Table C.

Groups used for Project Number 34R0165/84086. Hereafter designated Study 6.

Test group	Dose mg/kg/day	Volume of Doses ml/kg/day	Conc. in mg/100 ml	Number of Females
1. Cont.	0.5% CMC in water vehicle	5	0	25
2. Low (LDT)	200	5	4000	25
3. High(HDT)	400	5	8000	25

Table D.

Groups used for Project Number 92R0165/84088. Hereafter designated Study 8.

Test group	Dose mg/kg/day	Volume of Doses ml/kg/day	Conc. in mg/100 ml	Number of Females
1. Cont.	0.5% CMC in water vehicle	10	0	10
2. Low (LDT)	600	10	6000	10
3. High(HDT)	1000	10	10000	10

3. Analysis of Dosing Solutions: Analyses on the stability, homogeneity were stated to be carried out by the analytical laboratories of BASF (Dr. Schmidt). Analysis of the concentration of dosing suspensions were conducted twice during the dosing period (Dr. Pawliczek) and are reported in Tables E, F, G, and H.

Results - The test material in 0.5% CMC was found to be sufficiently stable if dosing solutions were prepared each day. Solutions were found to be 80% stable within 24 hours. A degradation product which is also a metabolite, was increased by the corresponding decrease in the concentration of the test substance. The concentrations of the dosing suspensions were 81% -83% of nominal at the lowest dose tested and the next higher dose level (Table E). These were the first analyses conducted and were in greater error probably because of inexperience of the analysist with the problems of analyzing Vinclozolin in CMC. Analyses conducted with more experience and at higher dose levels were 93%- 106% of nominal (Table F-H). Ordinarily, the Agency adjusts the LEL and NOEL by percentage deviation from nominal, however, this will not be done in this case for two reasons. 1) The dose levels analyzed later in the study which included a dose level of 50 mg/kg/day were 96-106% of nominal (Table F, G, and H) and indicated that the error (83% of nominal) noted in study 4 in the 50 mg/kg/day dose level was probably an analytical error and not an error in the dose level. In addition, the 15 mg/kg/day

dose level is sufficiently lower than the minimal effect level of 50 mg/kg/day to compensate for any error which may have occurred in the 50 mg/kg/day dose level. 2) The 50 mg/kg/day dose level was very close to the dose level which caused no effects as can be seen from the data and discussion on page 10 of this DER, i.e. the anal-genital distance was statistically significantly decreased at the 50 mg/kg/day dose level but anal-genital index, a better indicator of these effects, was only nominally decreased.

This reviewer has seen data from several testing laboratories indicating considerable difficulty with initial analytical results on test material suspended in carboxymethylcellulose and methylcellulose. The analytical concentrations become closer to 100% of nominal for analyses conduced after the testing laboratory gains experience with analyses in CMC or MC.

The stability data must be submitted.

Table E.
Concentration of dosing suspensions for number 4.

Dose level mg/kg/day	Nominal mg/ml	Average Analytical % of nominal	Range
15	3000	81%	61-104%
50	10000	83%	51-98%
150	30000	99%	87-108%

Table F.
Concentration of dosing suspensions for number 5.

Dose level mg/kg/day	Nominal mg/ml	Average Analytical % of nominal	Range
50	10000	99%	93-102%
100	20000	98%	92-103%
200	40000	104%	100-108%

Table G.
Concentration of dosing suspensions for number 6.

Dose level mg/kg/day	Nominal mg/ml	Average Analytical % of nominal	Range
200	40000	101%	98-104%
400	80000	106%	104-107%

Table H.
Concentration of dosing suspensions for number 8.

Dose level mg/kg/day	Nominal mg/ml	Average Analytical % of nominal	Range
600	60000	93%	86-100%
400	80000	101%	101-101%

4. Food and Water: - The food source was ground Kliba 343 rat/mouse/hamster feed supplied by Klingentalmuhle AG, CH-4303 Kaiseraugst, Switzerland. The water source and purity water was the purity of tap water and analyzed by the municipal water authority. Both were supplied ad libitum.

5. Statistics - The data were analyzed by the Department of Toxicology at BASF. All tests were reported at the 5% and 1% level of significance.

6. Quality assurance was signed by Dr. V. Schulz of the quality assurance unit on 3/22/85 for project 34R0165/84084, 3/22/89 for project 34R0165/84085, 3/22/89 for project 34R0165/84086, but the statement was not signed for project 43R0165/84088. However, since project 34R0165/84088 was unnecessary for the evaluation of the developmental toxicity of Vinclozolin in rats, a quality assurance statement for study 8 is unnecessary.

7. History - These four studies were conducted in response to a study conducted in Japan under Japanese guidelines for BASF Japan [K Takehara, M Itabashi, T Inoue and M Tajima, "Teratogenicity Study of Vinclozolin (BAS-352F) to Rats in Dietary Administration", conducted by Nippon Institute for Biological Science, 2221-1 Shin-machi, Ohme-shi, Tokyo 198, December 1979 for BASF Japan]. This study from Japan differed from EPA guideline studies essentially in that the test material was administered in the diet, and from gd 0 through 21, 11 days longer than OPP requirement of gd 6 through 15 (HED Document No. 007228). The four new studies were also conducted for a longer dosing period, 6 through 19, but by gavage. Interim reports (October, 1988) have already been evaluated (Document Number 007228, May 31, 1989). **These four studies demonstrated effects on the anal-genital distance in males, and verify the study results from Japan.**

The final reports of these four studies conducted by BASF to validate the effects noted in the study from Japan are the subject of this DER. This validation is reported in a series of studies designated by the BASF Study Number 89/0190; Report study # 89/090, 89/0091, 89/0092, and 89/0093 or projects # 34R0165/-84084, 34R0165/84085, 34R0165/ 84086, 92R0165/84088, respectively.

C. METHODS AND RESULTS: The numbered tables were copied from study report submitted.

Developmental Toxicity/83-3/Rat/BASF # 89-0190.

1. Observations - Animals were inspected daily and more frequently if needed for signs of toxicity and mortality.

Results - Toxicity - Unsteady gate was observed in a total of 1/10 animals on gd 13-15 and 18-19 at 600 mg/kg/day, and 7/10 animals by the end of gestation; 5/10 animals on gd 11 and 13, and 2/10 animals on gd 14 and 13 at the 1000 mg/kg/day dose level. These effects disappeared after gd 14 except in the 1 animals at 600 mg/kg/day and 1 animal at 1000 mg/kg/day. Piloerection was observed in 2/10 animals, and urine stained fur in 1/10 animals at 1000 mg/kg/day. Vaginal bleeding occurred in 1 animal on gd 13 only at 600 mg/kg/day. No other adverse observations were reported.

Mortality (Survival) - No unscheduled deaths were reported.

2. Body Weight - They were weighed on gd 0, 1, 3, 6, 8, 10, 13, 15, 17, 19, and 20. The body weight gain was determined between successive weighings.

Results - Body weights and body weight gain were variable but none appeared to demonstrate a dose related decrement or elevation. Statistically significant increases and decreases were noted, but no treatment related responses were noted even at 1000 mg/kg/day. Body weight gain was statistically significantly decreased on gd 8 to 10, but statistically significantly increased on gd 13 to 15 at 1000 mg/kg/day (Table 004 of study 8). On the other gestational days the body weights and weight gains alternated between nominally elevated and nominally decreased. At lower dose levels, statistically significant body weight gain elevations and decrements occurred but due to the inconsistencies and failure to exhibit body weight gain decrements at 1000 mg/kg/day, they probably were not dose related. However, it should be noted that in study 4 the body weight gain was nominally elevated through out gestation in the 50 and 150 mg/kg/day dose level, and statistically significantly elevated during gd 13-15 at both dose levels (Table 003 of study 4). In addition, a statistically significant body weight gain (111% of controls) occurred at gd 0-20 at the 150 mg/kg/day dose level (Table 004 of study 4). Although, these body weight gain increases may not be dose related, they could be indirectly related to effects seen on the adrenal in another study. Similar body weight gain increases, in addition to adrenal weight increases were seen in the dermal developmental toxicity study (MRID # 414130-01) at analogous dose levels. Adrenal weights were investigated only at the 600 and 1000 mg/ kg/day dose levels higher in this series of studies.

3. Food consumption - Food consumption was determined and mean daily intake was calculated. Efficiency was not determined in the submitted report. Food consumption was determined gd 0 to 1, 1 to 3, 3 to 6, 6 to 8, 8 to 10, 10 to 13, 13 to 15, 15 to 17, 17 to 19, and 19 to 20.

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Results - Food consumption was generally comparable to control values on the last one half of the gestational days. On gd 6 to 8 (88% of controls), 8 to 10 (64% of controls), and 10 to 13 (70% of controls) at 1000 mg/kg/day, food consumption was statistically significantly decreased. However, preliminary observations of the food consumption and body weight gain patterns did not indicate any dose related effects at the higher dose levels.

Relative efficiency of food utilization was not calculated because preliminary calculations indicated that the results were too variable.

4. Water consumption - Water consumption was determined during the same intervals as the body weight.

Results - Water consumption was statistically significantly different from controls from gestation day 0 to 6, about 113%, and from day 6 to day 13, about 74% of controls in the 1000 mg/kg/day dose group. The water consumption was nominally decreased from gd day 13 to 15 and nominally elevated during the remainder of gestation at the 1000 mg/kg/day dose level. However, no dose related effects appeared to occur in water consumption.

5. Blood was collected - Blood was collected from the retroorbital venus plexus. Blood was collected on gd 20. When a percent change is reported below in parentheses, it refers to percent of control values.

The CHECKED (X) parameters were examined.

a. Hematology -

X Hematocrit (HCT)*
X Hemoglobin (HGB)*
X Leukocyte count (WBC)*
X Erythrocyte count (RBC)*
X Platelet count*
X Reticulocytes (RETI)
Total plasma protein (TP)
Leukocyte differential count
X Mean corpuscular HGB (MCH)
X Mean corpuscular HGB conc. (MCHC)
X Mean corpuscular volume (MCV)

Results - Platelets were statistically significantly depressed at 150 mg/kg/day (92%) in study 4. The white blood cell count was statistically significantly depressed at 200 mg/kg/day in study 5, and statistically significantly elevated at 1000 mg/kg/day in study 8. There were no statistically significant differences in study 6. None of the effects showed any dose relationship or consistency, and thus, these effects may not be test material related.

6. Necropsy of Mothers and Fetal Examinations: Dams were sacrificed on gd 20. Pregnant uteruses were weighed and subtracted from the weight of the dam. The corpora lutea, the number of viable fetuses, dead fetuses, resorptions, and implantation sites were counted. Fetal weights were determined and malformations and variations were determined. The anal-genital distance and index was determined in fetuses from study 4, 6, and 8. The anal-

genital index was determined by measuring the distance from the center of the anal opening to the base of the genital tubercle divided by the fetal weight. The male fetuses in the 1000 mg/kg/day dose group looked like females, but on examination of the placement and appearance of the male gonads, they appeared to be superficially normal. On this basis the phenomenon was considered to be pseudohermaphroditism. Fetuses were stated to be examined according to the FIFRA guidelines. Fetuses were examined externally and after fixation in Bouin's solution for soft tissue anomalies by the method of Barrow and Taylor (1969) [J Morph. 127: 291-30-6]. After fixation in alcohol about one half the fetuses were examined for skeletal anomalies by the method of Dawson (1926) [Stain Technol. 1: 123].

a. Gross pathology on Mothers - No dose related effects were reported.

b. Results on Mothers - The carcass weight of dams, and the gravid uterus was not statistically significantly different from control values. Absolute and relative liver weights (Abs. 132-145% of control values) and adrenal weights (Abs. 220-280% of control values) were statistically significantly elevated at 600 and 1000 mg/kg/day in study 8. Organ weights were not determined at lower dose levels in the other studies of this series.

Reproduction data and corpora luteal counts, implantation loss, and post-implantation loss did not differ from control values.

c. Results of the Fetal Examination - The fetal anal-genital distances are reported in Table 015 of study 4, Table 015 of study 6, and Table 018 of study 8. The anal-genital distance was not determined in study 5. A statistically significant dose related decrease occurred in the anal-genital distance in male fetuses at 50 mg/kg/day and higher, and in the anal-genital index at 150 mg/kg/day and higher. No comment was made with regard to female fetuses, which may have also had undetected hormone related effects.

Fetal weights are statistically significantly depressed only at 1000 mg/kg/day in study 8 (Table 019). Early, late, and total resorptions did not differ from control values. The number of live male and females fetuses did not differ from control values, although at the 1000 mg/kg/day dose level, superficially there were no male fetuses. On soft-tissue examination, the incidence of dilated renal pelvis and hydroureter in fetuses and hydroureter in litters were each statistically significantly elevated at 400 mg/kg/day in study 6 (Table 023 of study 6). At the higher dose levels in study 8, statistically significant increases occurred only in hydroureter in fetuses at 600 mg/kg/day, but dilated renal pelvis was nominally elevated at 1000 mg/kg/day (Table 026 of study 8). However these results may not have been based on sufficient numbers of litters to give definitive results. These results were based on litters from 7, 5, and 8 dams in controls, 600, and 1000 mg/kg/day dose groups, respectively. Lower dose level groups contained 24 litters. In study 6

with 24 litters, statistically significant increases were seen in hydroureter. and dilated renal pelvis in fetuses at 400 mg/kg/day. The LEL for this effect should be considered 400 mg/kg/day and NOEL should be considered 200 mg/kg/day.

On skeletal examination, the incidence of fetuses with accessory 14th rib is statistically significantly increased, and the incidence in litters is nominally increased at 400 mg/kg/day in study 6 (Table 027 of study 6). The accessory 14th rib was statistically significantly increased at the 600 and 1000 mg/kg/day dose level in litters in study 8 (Table 030 of study 8). Other parameters were statistically significantly increased and some were statistically significantly decreased in fetuses, and fetuses and litters, but probably were not compound related. Even the increased incidence of 14th rib may not be treatment related because of the higher incidence noted in the controls than in dose groups of study 5, and the marginal increase seen in study 6 and 8. Thus the apparent effects on the 14th rib are equivocal. Statistically significant decreases occurred in ossification of the sternebrae in fetuses at 600 and 1000 mg/kg/day in study 8 (Table 032 of study 8).

D. DISCUSSION AND ABSTRACT:

Vinclozolin was administered orally by gavage (vehicle was 0.5% carboxymethylcellulose in water) to 25 rats/group at 0, 15, 50, and 150 mg/kg/day in study 4 (34R0165/8408**4**), at 0, 50, 100, 200 mg/kg/day in study 5 (34R0165/8408**5**), at 0, 200, 400 mg/kg/day in study 6 (34R0165/8408**6**), and to 10 rats/group at 0, 600, and 1000 mg/kg/day in study 8 (92R0165/8408**8**) from gestational day (gd) 6 through 19. At gd 20 the fetuses were investigated by appropriate methods outlined in OECD and FIFRA guidelines. Maternal toxicity was demonstrated at 600 and 1000 mg/kg/day by the statistically significant increase in absolute and relative adrenal and liver weight in study 8, the only study where organ weights were determined. No histology was conducted on the organs, but other studies have demonstrated lipid accumulation in the adrenals, and centrilobular cloudiness of the liver. In addition, a dermal developmental study (MRID # 414130-01) has indicated adrenal and liver weight increases occurred at 180 mg/kg/day and higher. Statistically significant increases and decreases occurred in the body weight gain and in food consumption with no apparent dose relatedness in any of the studies. The relative efficiency of food utilization was too variable to be definitive.

Statistically significant male and female fetal body weight decrements occurred at 1000 mg/kg/day in study 8. These weight decrements are considered test material related.

A statistically significant increase occurred in pseudohermaphroditism among male fetuses. The term pseudohermaphroditism was used to describe the effect because these males exhibited decreased anal-genital distances, but exhibited superficially normal internal testes. The anal-genital distance in male fetuses was statistically significantly decreased at 50 mg/kg/day and

higher in study 4, 6, and 8 (The anal-genital index was statistically significantly depressed at 150 mg/kg/day and higher). The anal-genital distance and index were not determined in study 5. The response was dose related. Although anal-genital index was not statistically significantly depressed at 50 mg/kg/day, it was nominally depressed. Considering the significantly depressed anal-genital distance at 50 mg/kg/day and higher and the nominally depressed anal-genital index at 50 mg/kg/day, the NOEL for this study was considered to be 15 mg/kg/day, the LDT. These results are consistent with hormonal or anti-hormonal effects from the test material.

Soft tissue examination of fetuses indicated that increased incidence occurred in dilated renal pelvis and hydroureter at 400 mg/kg/day in study 6. At higher dose levels in study 8, the incidence of dilated renal pelvis and hydroureter was nominally increased. The failure of the dilated renal pelvis, and hydroureter to be significantly increased in study 8 was attributed to the fewer litters used (7, 5, and 8 in controls, 600, and 1000 mg/kg/day). The NOEL for these renal effects is considered to be 200 mg/kg/day.

Skeletal examination of fetuses indicated increased incidence of accessory 14th rib at 400 mg/kg/day and in fetuses and litters at 600, and 1000 mg/kg/day. These effects on the 14th rib may be related to dose administration. Evaluation of the Preliminary Study suggested a dose related increase in 14th ribs at these high dose levels. No other dose related effects were reported.

Summary:

Four preliminary studies were conducted in rats to determine the potential of Vinclozolin to cause developmental effects. In the combined studies doses were administered by gavage at 0, 15, 50, 100, 150, 200, 400, 600, 1000 mg/kg/day from gestational day 6 to 19. Maternal toxicity was demonstrated at 600 and 1000 mg/kg/day by the statistically significant increase in absolute and relative adrenal and liver weight at 600, and 1000 mg/kg/day, the only dose levels where organ weights were determined. No histology was conducted on the organs, but other studies have demonstrated lipid accumulation in the adrenals, and centrilobular cloudiness of the liver. No dose related body weight effects occurred in dams. A dose related statistically significant increase occurred in psemdohermaphroditism among male fetuses at the 50 mg/kg/day dose level and above. The term pseudohermaphroditism was used to describe the effect because these males exhibited decreased anal-genital distances, but exhibited superficially normal internal testes. At higher dose levels renal and skeletal effects were noted at 400 mg/kg/day.
No effects were noted at 15 mg/kg/day.

DER for Developmental Toxicity/89/0190/34R0165/84084/84085/84086/84088/B:\VINCLV23.23C\DDEV4COM.FUL/DAnderson/4/22/90.

2-JAN-89

84084

Study 4

PROJECT NO. 34HU165/84084: PRENATAL TOXICITY STUDY IN RATS — TABLE 1 — 003
ORAL ADMINISTRATION (GAVAGE)
MEAN MATERNAL BODY WEIGHT CHANGE DURING GESTATION -- GRAMS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 15 MG/KG BW/DAY	TEST GROUP 2 60 MG/KG BW/DAY	TEST GROUP 3 150 MG/KG BW/DAY
DAYS 0 TO 1	MEAN	0.8	1.6	1.2	2.2
	S.D.	3.23	3.02	3.32	3.02
	N	24	23	24	24
DAYS 1 TO 3	MEAN	10.8	9.8	10.0	9.8
	S.D.	2.58	4.53	3.44	3.78
	N	24	23	24	24
DAYS 3 TO 6	MEAN	11.0	13.0	13.1	14.0a
	S.D.	4.03	7.03	4.57	3.38
	N	24	23	24	24
DAYS 6 TO 8	MEAN	8.1	8.8	8.4	10.2
	S.D.	5.26	5.34	3.36	3.08
	N	24	23	24	24
DAYS 8 TO 10	MEAN	10.8	10.8	11.7	12.8
	S.D.	3.33	2.88	3.00	4.08
	N	24	23	24	24
DAYS 10 TO 13	MEAN	10.7	10.2	10.8	10.8
	S.D.	6.08	4.28	4.46	2.90
	N	24	23	24	24
DAYS 13 TO 15	MEAN	11.9	13.5	12.9	13.9
	S.D.	3.28	3.66	6.68	4.08
	N	24	23	24	24
DAYS 15 TO 17	MEAN	17.4	20.1	21.7a	21.1a
	S.D.	7.70	4.22	3.62	3.20
	N	24	23	24	24
DAYS 17 TO 19	MEAN	30.2	28.6	30.9	31.1
	S.D.	10.65	6.21	7.27	8.84
	N	24	23	24	24
DAYS 19 TO 20	MEAN	14.8	15.8	16.0	16.2
	S.D.	6.28	3.37	3.90	5.05
	N	24	23	24	24

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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2-JAN-89

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Study #

TABLE 1 004

PROJECT NO. 34ND165/84084: PRENATAL TOXICITY STUDY IN RATS
ORAL ADMINISTRATION (GAVAGE)
MEAN MATERNAL BODY WEIGHT CHANGE DURING GESTATION - GRAMS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 15 MG/KG BW/DAY	TEST GROUP 2 50 MG/KG BW/DAY	TEST GROUP 3 150 MG/KG BW/DAY
DAYS 0 TO 6	MEAN	22.6	24.4	25.2	28.0
	S.D.	6.94	8.24	6.87	6.38
	N	24	23	24	24
DAYS 6 TO 10	MEAN	98.2	100.3	100.1	107.3
	S.D.	20.10	13.42	13.12	14.19
	N	24	23	24	24
DAYS 0 TO 20	MEAN	130.5	140.5	147.3	150.4*
	S.D.	23.76	18.18	18.00	21.74
	N	24	23	24	24

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = P<0.05; ** = P<0.01.

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Study 4

TABLE 1 015

PROJECT NO. 34R0165/84084: PRENATAL TOXICITY STUDY IN RATS
ORAL ADMINISTRATION (GAVAGE)
MEAN PLACENTAL WEIGHTS, MEAN AG DISTANCE AND AG INDEX

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 15 MG/KG BW/DAY	TEST GROUP 2 [illegible]/KG BW/DAY	TEST GROUP 3 150 MG/KG BW/DAY
PLACENTAL WEIGHTS UNITS: GRAMS					
of all Viable Fetuses	MEAN	0.43	0.42	0.42	0.42
	S.D.	0.060	0.035	0.035	0.041
	N	24	23	24	24
of Male Fetuses	MEAN	0.43	0.43	0.42	0.41
	S.D.	0.060	0.038	0.037	0.031
	N	24	23	24	23
of Female Fetuses	MEAN	0.41	0.41	0.42	0.42
	S.D.	0.036	0.036	0.036	0.044
	N	22	23	24	24
AG DISTANCE UNITS: MM					
of all Viable Fetuses	MEAN	1.6	1.5	1.5	1.36
	S.D.	0.31	0.31	0.23	0.24
	N	23	23	24	24
of Male Fetuses	MEAN	2.2	2.2	2.16	1.80
	S.D.	0.09	0.12	0.10	0.16
	N	23	22	24	21
of Female Fetuses	MEAN	1.0	1.0	0.9	0.9
	S.D.	0.08	0.08	0.08	0.07
	N	20	23	24	24
AG INDEX					
of all Viable Fetuses	MEAN	0.42	0.40	0.40	0.340
	S.D.	0.082	0.087	0.064	0.049
	N	23	23	24	24
of Male Fetuses	MEAN	0.55	0.55	0.53	0.460
	S.D.	0.047	0.040	0.037	0.034
	N	23	22	24	21
of Female Fetuses	MEAN	0.26	0.25	0.25	0.25
	S.D.	0.036	0.023	0.031	0.024
	N	20	23	24	24

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05, b = P<0.01.

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Study 6

PROJECT NO. 34H0185/84086: PRENATAL TOXICITY STUDY IN RATS
ORAL ADMINISTRATION (GAVAGE)
MEAN PLACENTAL WEIGHTS, MEAN AG DISTANCE AND AG INDEX

TABLE 1 016

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 200 MG/KG BW/DAY	TEST GROUP 2 400 MG/KG BW/DAY
PLACENTAL WEIGHTS UNITS: GRAMS				
of all Viable Fetuses	MEAN	0.43	0.43	0.43
	S.D.	0.041	0.060	0.060
	N	28	22	24
of Male Fetuses	MEAN	0.43	0.43	0.43
	S.D.	0.047	0.063	0.060
	N	28	22	24
of Female Fetuses	MEAN	0.42	0.42	0.43
	S.D.	0.041	0.047	0.049
	N	28	22	24
AG DISTANCE UNITS: MM				
of all Viable Fetuses	MEAN	1.7	1.3b	1.2b
	S.D.	0.28	0.10	0.11
	N	28	22	24
of Male Fetuses	MEAN	2.3	1.8b	1.4b
	S.D.	0.11	0.10	0.10
	N	28	22	24
of Female Fetuses	MEAN	1.0	1.0	1.0
	S.D.	0.09	0.10	0.12
	N	28	22	24
AG INDEX				
of all Viable Fetuses	MEAN	0.43	0.33b	0.32b
	S.D.	0.082	0.046	0.037
	N	28	22	24
of Male Fetuses	MEAN	0.57	0.40b	0.36b
	S.D.	0.038	0.082	0.036
	N	28	22	24
of Female Fetuses	MEAN	0.26	0.26	0.27
	S.D.	0.028	0.036	0.040
	N	28	22	24

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01

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Study 6

PROJECT NO. 34R0165/84086: PRENATAL TOXICITY STUDY IN RATS
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF FETAL SOFT TISSUE VARIATIONS

TABLE 023

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 200 MG/KG BW/DAY	TEST GROUP 2 400 MG/KG BW/DAY
Litters Evaluated	N	26	22	24
Fetuses Evaluated	N	165	142	164
Live	N	165	142	164
Dead	N	0	0	0
DILATED RENAL PELVIS				
Fetal Incidence	N	68	75	98b
	%	41	53	60
Litter Incidence	N	24	21	24
	%	86	95	100
HYDROURETER				
Fetal Incidence	N	19	27	55b
	%	12	19	34
Litter Incidence	N	8	13	18b
	%	32	59	75
TOTAL FETAL SOFT TISSUE VARIATIONS				
Fetal Incidence	N	68	75	98b
	%	41	53	60
Litter Incidence	N	24	21	24
	%	86	95	100

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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Study 6

PROJECT NO. 34R0165/84086: PRENATAL TOXICITY STUDY IN RATS
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF FETAL SKELETAL VARIATIONS

TABLE 1 027

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 200 MG/KG BW/DAY	TEST GROUP 2 400 MG/KG BW/DAY
Litters Evaluated	N	25	22	24
Fetuses Evaluated	N	172	154	178
Live	N	172	154	178
Dead	N	0	0	0
STERNEBRA(E) OF IRREGULAR SHAPE				
Fetal Incidence	N	58	43	30a
	%	34	28	22
Litter Incidence	N	21	18	20
	%	84	82	83
STERNEBRA(E) BIPARTITE				
Fetal Incidence	N	5	8	2
	%	2.9	5.2	1.1
Litter Incidence	N	2	7	2
	%	8.0	32	8.3
ACCESSORY STERNEBRA				
Fetal Incidence	N	1	0	0
	%	0.6	0.0	0.0
Litter Incidence	N	1	0	0
	%	4.0	0.0	0.0
ACCESSORY 14TH RIB(S)				
Fetal Incidence	N	1	5	8a
	%	0.6	3.9	4.5
Litter Incidence	N	1	3	5
	%	4.0	14	21
RUDIMENTARY CERVICAL RIB(S)				
Fetal Incidence	N	7	2	1a
	%	4.1	1.3	0.6
Litter Incidence	N	6	1	1
	%	24	4.6	4.2
13TH RIB(S) SHORTENED				
Fetal Incidence	N	18	7	30
	%	10	4.5	17
Litter Incidence	N	12	3a	3a
	%	48	14	13

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05, b = P<0.01.

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Study 8

TABLE 004

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PROJECT NO. 82N0180/84088. PRENATAL TOXICITY STUDY IN RATS
ORAL ADMINISTRATION (GAVAGE) - TEST STUDY
MEAN MATERNAL BODY WEIGHT CHANGE DURING GESTATION -- GRAMS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 600 MG/KG BW/D	TEST GROUP 2 1000 MG/KG BW/D
DAYS 0 TO 1	MEAN	3.0	2.6	4.0
	S.D.	3.41	2.38	2.94
	N	7	7	8
DAYS 1 TO 3	MEAN	10.0	14.1	12.8
	S.D.	4.83	3.88	2.72
	N	7	7	8
DAYS 3 TO 6	MEAN	11.8	15.8	14.0
	S.D.	2.52	4.35	2.57
	N	7	7	8
DAYS 6 TO 8	MEAN	7.6	6.2	3.2
	S.D.	1.98	2.71	6.11
	N	7	7	8
DAYS 8 TO 10	MEAN	10.0	4.3	-4.3a
	S.D.	4.11	9.78	11.65
	N	7	7	8
DAYS 10 TO 13	MEAN	14.5	10.9	10.2
	S.D.	4.21	13.61	16.52
	N	7	7	8
DAYS 13 TO 15	MEAN	13.1	13.8	21.7a
	S.D.	3.67	6.22	6.62
	N	7	7	8
DAYS 15 TO 17	MEAN	21.4	20.9	26.3
	S.D.	6.08	11.88	8.31
	N	7	7	8
DAYS 17 TO 19	MEAN	31.3	21.2	37.1
	S.D.	4.74	13.12	11.64
	N	7	7	8
DAYS 19 TO 20	MEAN	17.6	13.3	14.8
	S.D.	5.50	7.11	7.28
	N	7	7	8

SIGNIFICANTLY DIFFERENT FROM CONTROL: a - P<0.05, b - P<0.01.

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Study 8

TABLE 1 018

PROJECT NO. 92R0165/84088: PRENATAL TOXICITY STUDY IN RATS
ORAL ADMINISTRATION (GAVAGE) - TEST STUDY
MEAN PLACENTAL WEIGHTS, MEAN AG DISTANCE AND AG INDEX

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 600 MG/KG BW/D	TEST GROUP 2 1000 MG/KG BW/D
PLACENTAL WEIGHTS UNITS: GRAMS				
of all Viable Fetuses	MEAN	0.40	0.41	0.40
	S.D.	0.036	0.025	0.032
	N	7	5	8
of Male Fetuses	MEAN	0.41	0.41	0.40
	S.D.	0.036	0.031	0.041
	N	7	5	8
of Female Fetuses	MEAN	0.39	0.40	0.40
	S.D.	0.037	0.028	0.030
	N	7	5	8
AG DISTANCE UNITS: MM				
of all Viable Fetuses	MEAN	1.8	1.3b	1.1b
	S.D.	0.22	0.12	0.06
	N	7	5	8
of Male Fetuses	MEAN	2.3	1.3b	1.2b
	S.D.	0.09	0.13	0.08
	N	7	5	8
of Female Fetuses	MEAN	1.1	1.1	1.1
	S.D.	0.04	0.09	0.04
	N	7	4	8
AG INDEX				
of all Viable Fetuses	MEAN	0.46	0.33b	0.31b
	S.D.	0.052	0.031	0.024
	N	7	5	8
of Male Fetuses	MEAN	0.58	0.35b	0.32b
	S.D.	0.025	0.039	0.022
	N	7	5	8
of Female Fetuses	MEAN	0.29	0.30	0.31
	S.D.	0.017	0.029	0.029
	N	7	4	8

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05, b = P<0.01

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Study 8

TABLE 019

PROJECT NO. 82R0165/84088, PRENATAL TOXICITY STUDY IN RATS
ORAL ADMINISTRATION (GAVAGE) - TEST STUDY
MEAN FETAL BODY WEIGHTS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 600 MG/KG BW/D	TEST GROUP 2 1000 MG/KG BW/D
FETAL WEIGHTS UNITS: GRAMS				
of all Viable Fetuses	MEAN	3.8	3.9	3.56
	S.D.	0.08	0.09	0.17
	N	7	5	8
of Male Fetuses	MEAN	3.9	3.9	3.66
	S.D.	0.09	0.08	0.21
	N	7	5	8
of Female Fetuses	MEAN	3.7	3.8	3.46
	S.D.	0.08	0.12	0.19
	N	7	5	8

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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Study 8

PROJECT NO 92H0165/84088: PRENATAL TOXICITY STUDY IN RATS
ORAL ADMINISTRATION (GAVAGE) - TEST STUDY
SUMMARY OF FETAL SOFT TISSUE VARIATIONS

TABLE 1 [illegible]

		TEST GROUP 0 CONTROL (ML	TEST GROUP 1 600 MG/KG BW/D	TEST GROUP 2 1000 MG/KG BW/D
Litters Evaluated	N	7	5	5
Fetuses Evaluated	N	45	32	8
Live	N	45	32	8
Dead	N	0	0	0
DILATED RENAL PELVIS				
Fetal Incidence	N	20	16	2
	%	44.4	50.0	25.0
Litter Incidence	N	7	5	2
	%	100.0	100.0	100.0
HYDROURETER				
Fetal Incidence	N	4	11	1
	%	8.9	34.4	12.5
Litter Incidence	N	3	5	1
	%	42.9	100.0	100.0
TOTAL FETAL SOFT TISSUE VARIATIONS				
Fetal Incidence	N	20	18	2
	%	44.4	56.3	25.0
Litter Incidence	N	7	5	2
	%	100.0	100.0	100.0

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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Study 8

TABLE 030

PROJECT NO. 92R0165/84088: PRENATAL TOXICITY STUDY IN RATS
ORAL ADMINISTRATION (GAVAGE) - TEST STUDY
SUMMARY OF FETAL SKELETAL VARIATIONS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 600 MG/KG BW/D	TEST GROUP 2 1000 MG/KG BW/D
Litters Evaluated	N	7	5	8
Fetuses Evaluated	N	61	34	57
Live	N	61	34	57
Dead	N	0	0	0
ACCESSORY LUMBAR VERTEBRA				
Fetal Incidence	N	0	1	0
	%	0.0	2.9	0.0
Litter Incidence	N	0	1	0
	%	0.0	20.0	0.0
STERNEBRA(E) OF IRREGULAR SHAPE				
Fetal Incidence	N	28	8b	19a
	%	56.9	23.5	33.3
Litter Incidence	N	7	4	7
	%	100.0	80.0	87.5
STERNEBRA(E) BIPARTITE				
Fetal Incidence	N	3	0	0
	%	5.9	0.0	0.0
Litter Incidence	N	2	0	0
	%	28.6	0.0	0.0
13TH RIB(S) SHORTENED				
Fetal Incidence	N	8	0a	0b
	%	15.7	0.0	0.0
Litter Incidence	N	4	0	0a
	%	57.1	0.0	0.0
ACCESSORY 14TH RIB(S)				
Fetal Incidence	N	0	3	5
	%	0.0	8.8	8.8
Litter Incidence	N	0	3a	3
	%	0.0	60.0	37.5
RUDIMENTARY CERVICAL RIB(S)				
Fetal Incidence	N	2	0	0
	%	3.9	0.0	0.0
Litter Incidence	N	1	0	0
	%	14.3	0.0	0.0

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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Study 8

TABLE 0.12

PROJECT NO. 92R0165/84088: PRENATAL TOXICITY STUDY IN RATS
ORAL ADMINISTRATION (GAVAGE) - TEST STUDY
SUMMARY OF FETAL SKELETAL RETARDATIONS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 600 MG/KG BW/D	TEST GROUP 2 1000 MG/KG BW/D
Litters Evaluated	N	7	5	8
Fetuses Evaluated	N	51	34	57
Live	N	51	34	57
Dead	N	0	0	0
RUDIMENTARY VERTEBRAL BODY/BODIES DUMBBELL-SHAPED (SYMMETR.)				
Fetal Incidence	N	6	2	6
	%	9.8	5.9	10.5
Litter Incidence	N	3	2	6
	%	42.9	40.0	75.0
STERNEBRA(E) NOT OSSIFIED				
Fetal Incidence	N	10	6	4
	%	19.6	17.6	7.0
Litter Incidence	N	4	2	3
	%	57.1	40.0	37.5
STERNEBRA(E) ONLY ONE OSSIFICATION CENTER				
Fetal Incidence	N	18	6	9a
	%	35.3	17.6	15.8
Litter Incidence	N	5	4	3
	%	88.7	80.0	37.5
STERNEBRA(E) INCOMPLETELY OSSIFIED OR REDUCED IN SIZE				
Fetal Incidence	N	16	20	60
	%	31.4	5.9	10.5
Litter Incidence	N	5	2	5
	%	71.4	40.0	62.5
TOTAL FETAL SKELETAL RETARDATIONS				
Fetal Incidence	N	39	140	230
	%	76.5	41.2	40.4
Litter Incidence	N	7	5	7
	%	100.0	100.0	87.5

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01

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